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10/563,683	10/04/2006	Mark T. Gladwin	4239-67618-07	3225

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EXAMINER	
PAGONAKIS, ANNA	
ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
07/27/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/563,683	GLADWIN ET AL.	
	Examiner	Art Unit	
	ANNA PAGONAKIS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *5-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 sheet; 3/26/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 3/26/2010 has been received and entered into the present application.

As reflected by the attached, completed copy form PTO/SB/08A (one page total), the Examiner has considered the cited references.

Given that the entirety of the rejections set forth are not identical to those previously made of record, the Examiner is issuing the Office Action for Applicant's consideration prior to granting a telephonic interview.

Applicant's arguments filed 3/26/2010 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Status of Claims

Claims 1-18 are pending.

Claims 5-12 remain withdrawn.

Claims 1-4 and 13-18 are currently under consideration and the subject matter of the current Office Action.

Rejection necessitated by amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, has possession of the claimed invention.

Present claim 16 is directed to a method wherein the non-acidified sodium nitrite is administered to the subject in an amount and for a sufficient period of time to reach a circulating concentration in blood of the subject no more than about 25 microM, thereby treating or ameliorating the condition.

In particular, the specification and claims as originally fail to provide adequate written description for the newly added claim 16. Upon review of the instant disclosure, there seems to be no disclosure of claim 16. While it is recognized that adequate written description of a limitation is not required to be stated *in haec verba* in the specification or claims as originally filed, adequate written support for all claim limitations must arise from either an explicit or an implicit suggestion by the disclosure to show that such a concept as now claimed was actually in possession of the Applicant at the time of the invention.

MPEP §2163 states, "The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test of sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir.

1983))…Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)."

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

Response to Applicant's Remarks

Applicant alleges that the concentration of circulating blood listed in claim 16 is found implicitly in the disclosure, specifically point to the concentration being 221.82 uM as well as 30 uM and 15 uM. Additionally, Applicant guides the Examiner to the ranges about 0.6 to about 200 uM as well as the concentrations of no more than about 100 uM; no more than 50 uM; no more than 20 uM; no more than 16 uM or less than about 16 uM. This is not found persuasive. Though Applicant seems to have support for the above cited ranges, the instantly claimed subgenus dose/range is not specifically supported by the above mentioned ranges. Applicant does not implicitly state "no more than 25 uM." Firstly, the first concentration amount provided is almost 10 times than that found in instant claim 16. Applicant points to two different blood concentrations of 30 uM and 15 uM in support of "no more than 25 uM", however, Applicant has not pointed to where the "at least about" of the claimed range can be found in the instant specification.

Priority

This application claims benefit of of provisional application 60/485,959 filed 7/9/2003 and 60/511,244 filed 10/14/2003.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional

application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, 60/485,959 filed 7/9/2003 as well as 60/511,244 filed 10/14/2003., fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. All claims are not adequately supported or enabled by the prior-filed applications for a method for treating or ameliorating a condition selected from hepatic or cardiac or brain ischemia-reperfusion injury; pulmonary hypertension or cerebral artery vasospasm in a subject by decreasing blood pressure and/or increasing vasodilation in the subject, the method comprising administering *non-acidified* sodium nitrite to the subject to decrease the blood pressure and/or increase vasodilation in the subject, thereby treating or ameliorating the condition.

It is noted that Applicant is not entitled to the priority date in these application for all claims in the instant claim set because the information contained within the previous referred filings does not support the granting of an earlier filing date. There is no instance, throughout the specification, of any calculation of any ratio.

Applicant's Remarks

Applicant alleges that PCT/US2004/22232 teaches "nitrite does not need to be applied in an acidified condition..." and the recitation of "non-acidified nitrite salt" on page 4, lines 5-12. Applicant alleges that provisional application 60/511,244 teaches (i) "the vasodilatory property of nitrite during basal blood flow conditions...when...pH are not exceedingly low, was unexpected and (ii) the buffered saline solution at a pH of about 7-8 and provisional application 60/485, 959 teaches nitrite solutions of pH 7.0-7.4 and that the teachings provide support for non-acidified sodium nitrite. This is not found persuasive. Per Applicant's guidance to the above teachings, it does not seem that the disclosures teach the limitation "non-acidified *sodium* nitrite." Further, 60/511,244 teaches "pH... not exceedingly low" is

vague while both 60/485,959 and 60/511,244 teaches a neutral pH, not a basic or neutral pH which Applicant defines as non-acidified in the response filed on 3/26/2010 (page 8, last two lines). Finally, it should be noted that Applicant merely seems to define, as state above, a composition comprising sodium nitrite, wherein the composition comprises a "basic" pH. However, the disclosures as filed do not seem to define what is meant by "non-acidified sodium nitrite."

Rejections necessitated by amendment:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al. (British Journal of Pharmacology, April 2003; of record) in view of Goldfrank et al. (Goldfrank's Toxicological Emergencies 7th Edition, 2002, page 1511) and Remington's Pharmaceutical Science (page 420-425, 1980).

Webb et al. teach a method of treating cardiac ischemia-reperfusion (I/R) injury with administration via infusion of 10-1000 uM of inorganic nitrite. It was concluded that the production of

nitric oxide protected against I/R injury as such may have an important therapeutic role in myocardial infarction. It should be noted that inorganic sodium nitrite, as stated in the Office Action mailed on 12/28/2009 on page 6, line 1, is interpreted to meet the claim.

Webb et al. is silent on the use of the salt, sodium nitrite and the administration of sodium nitrite in vivo via intravenous, intramuscular, rectal, ex vivo, intraocular, intraperitoneal, intraarterial, subcutaneous, inhalation and into cardiopulmonary bypass circuit.

Goldfrank et al. teach that administration of nitrite, such as sodium nitrite, induces vasodilation and enhances organ blood flow via denitration with subsequent release of nitric oxide (page 1511, left column). Further, the intravenous injection of sodium nitrite results is taught (page 1511, right column).

Remington's Pharmaceutical Sciences teaches that drugs may be formulated into salts to modify the duration of a drug, to modify the transportation and distribution of the drug in the body, to reduce toxicity and to overcome difficulties in pharmaceutical formulation procedures or in the dosage form itself (see column 2, page 424, first paragraph).

One of ordinary skill in the art would have been motivated to use intravenous as the route of administration because this route of administration is known to effective in administering sodium nitrite. Goldfrank et al. teach intravenous administration which provides the vasodilator to the systemic circulation. Additional forms of administration such as intravenous, intramuscular, rectal, ex vivo, intraocular, intraperitoneal, intraarterial, subcutaneous, inhalation and into a cardiopulmonary bypass circuit are obvious to one of ordinary skill in the art of medicine.

It would have been prima facie obvious to the skilled artisan by any one or more of these factors to formulate nitrite into a pharmaceutical acceptable salt, such as sodium nitrite, to enhance the pharmacokinetic parameters of the drug or to reduce the toxicity in order to facilitate administration in vivo. Further, when administered in vivo via infusion, the sodium nitrite would contact the blood. Finally, one of ordinary skill in the art would have had a reasonable expectation that the therapeutic

benefit of the agent in salt form would have the same or substantially similar to that of the agent itself.

With regard to claim 16-18, it is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claims 1-3 and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shaw et al. (US 4,650,484) in view of Goldfrank et al. (Goldfrank's Toxicological Emergencies 7th Edition, 2002, page 1511).

Shaw et al. disclose methods for treating **ischemic conditions** in a patient having such a condition by administration of a therapeutically effective amount of a vasodilator internally and transdermally to treat the condition (Abstract and claims 1-13). Shaw et al. teach **buccal** administration to get the vasodilator into the systemic circulation which means that it contacts the blood (claim 7). The nitrite, therefore, reacts in the presence of hemoglobin in the subject to release nitric oxide. **Sodium nitrite**, which is not acidified, is specifically named as a vasodilator in a finite list of vasodilators (column 2, lines 35-45). The method is to increase the supply of oxygen to the tissue such as the heart, which would be an ischemic heart (ischemic cardiac tissue and hence a cardiovascular condition) (column 2, lines 51-68). The vasodilator is administered with another agent, which is another vasodilator (claim 1).

Shaw et al. is silent on the route of administration selected from the group consisting of intravenous, intramuscular, rectal, ex vivo, intraocular, intraperitoneal, intra-arterial, subcutaneous, inhalation and into a cardiopulmonary bypass circuit.

Goldfrank et al. teach that administration of nitrite, such as sodium nitrite, induces vasodilation and enhances organ blood flow via denitration with subsequent release of nitric oxide (page 1511, left column). Further, the intravenous injection of sodium nitrite results is taught (page 1511, right column).

One of ordinary skill in the art would have been motivated to use injection as the route of administration because Shaw et al. is directed to getting the vasodilator into the systemic circulation. Goldfrank et al. teach intravenous administration which provides the vasodilator to the systemic circulation. Additional forms of administration such as intravenous, intramuscular, rectal, ex vivo, intraocular, intraperitoneal, intraarterial, subcutaneous, inhalation and into a cardiopulmonary bypass circuit are obvious to one of ordinary skill in the art of medicine especially when Shaw et al. is directed to getting the vasodilator into the systemic circulation.

With regard to claim 16-18, it is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shaw et al. (US 4,650,484) in view of Goldfrank et al. (Goldfrank's Toxicological Emergencies 7th Edition, 2002, page 1511) as applied to claims 1-3 and 13-18 above ***or alternatively*** over Webb et al. (British Journal of Pharmacology, April 2003) in view of Goldfrank et al. (Goldfrank's Toxicological Emergencies 7th Edition, 2002, page 1511) and Remington's Pharmaceutical Science (page 420-425, 1980) as applied to claims 1-3 and 13-18, and further in view of Modin et al. (Acta Physiol Scand 2001).

The combination of Shaw et al. (US 4,650,484) in view of Goldfrank et al. (Goldfrank's Toxicological Emergencies 7th Edition, 2002, page 1511) is set forth supra. The combination differs by being silent on the circulating concentration of 0.6 to 240 microM.

Modin et al. teach that nitric oxide is derived from nitrite (title) and that physiologically relevant concentrations of nitrite evoke vasodilation (page 13, right column Discussion; and page 15, left column last paragraph). Modin et al. teach that the relaxatory effect of nitrite was increased at pH 6.6 over neutral pH (Abstract). Thus Modin et al. teach that **non-acidified nitrite** also has relaxatory effects similar to "acidified" nitrite (see figures 1, 2, figure 5 and respective discussion in the text). Modin et al. administered various amounts of **sodium nitrite** but noted a threshold response of **10 microM** and near relaxation to basal tone at 1000 microM for the non-acidified sodium nitrite (page 11, Results). Modin et al. teach adding additional agents (ascorbic acid) to enhance the effect of the sodium nitrite (Abstract) Modin et al. conclude that inorganic nitrite evokes vasodilation most likely through nitric oxide release and that this effect is increased if the pH of the environment is reduced to levels normally found in tissues during **ischemia**/hypoxia (page 15, last paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use sodium nitrite within the range instantly claimed. One of ordinary skill in the art would have been motivated to do this because Shaw et al. teach *a therapeutically effective amount* to the systemic circulation to treat an ischemic condition in a patient and Modin et al. suggest how much sodium nitrite would be beneficial for use in tissues during ischemia. Modin et al. also indicate that human plasma has 0.45 microM nitrite and human serum has 6.6 microM nitrite (page 14, left column) so it is obvious to administer an amount of nitrite that would increase the plasma and serum concentration above the basal level for a therapeutic effect. It is merely routine optimization to obtain a circulating concentration.

It is obvious from the above teachings that Shaw et al. expressly contemplates variation in the dosage amounts and specifically acknowledges that such a matter was well within the skill of the artisan at the time of the invention and would not have required undue experimentation or have been outside the realm of knowledge generally available to the skilled artisan. Factors that would have been taken into consideration when making such a determination would have included, but not have been limited to, the age, weight, sex, diet and medical condition of the patient, severity of the disease, route of administration, pharmacological considerations, e.g., activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen and/or schedule of administration that would have actually been employed would have been expected to vary widely and, in the absence of evidence to the contrary, would not have been inconsistent with that which is presently claimed.

Applicant's Remarks

It should be noted that solely arguments not previously addressed with be addressed herein as not to burden the record.

Applicant alleges that the problem with the aortic ring bioassay disclosed by Modin et al., per the Lunderberg declaration, is that the experiments are performed without the presence of blood. Specifically, Applicant alleges that the Lundberg references teaches that the findings are not considered predictive that similar concentrations of inorganic nitrite would cause a vasodilatory effect under non-acidic conditions in vivo. Applicant is guided to MPEP 716.0(c)III which states: "In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. *Ashland Oil, Inc. v. Delta Resins*

& Refractories, Inc., 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986). Below is a sampling of what is taught in the art with regard to aortic ring bioassays:

(i) U.S. 6,153,186 teaches the use of aortic ring bioassays and that this data is fully commensurate with the in vivo findings (column 7, lines 64-65);

(ii) U.S. 5,436,271 teaches the use of rat aortic rings to test the effect of N-(hydrazinoiminomethyl)-L-lysine and further teaches of the compound for treatment in a subject (column 9, lines 42-45 and claim 1);

(iii) U.S. 6,110,453 teaches that Fig. 3 illustrates the time course of vascular relaxation when different doses of the poly-bound nitric oxide-releasing composition is exposed to the aortic ring, causes relaxation, then withdrawn from the organ bath, allowing restriction to occur, then reintroduced into the organ bath, causing the vessel to dilate again. It is concluded that the experiment illustrates the pharmacological effects of the polymer-bound nitric oxide/nucleophile composition which is particularly advantageous to localize the effects of nitric oxide release to a specific target organ (column 3, last full paragraph and column 4, lines 1-3).

(iv) Gladwin et al. (Free Radical Biology & Medicine, available online 1/4/2004). The primary inventor of the instant application states in the instant article (page 710, column bridging column 2 to page 711, column 1, first paragraph):

> "mechanisms proposed for the in vivo conversion of nitrite to NO include enzymatic reduction by xanthine oxidoreductase and nonenzymatic disproportionation/acidic reduction…. Indeed, *consistent* with oxygen- and pH- sensitive chemistry, hypoxia and acidosis potentiate NO generation and vasodilation from both nitrite and NO donors in *aortic ring bioassay* and lung perfusion bioassay systems (emphasis added)."

Though, the opinion of the declarants has been noted, the art including the primary inventor clearly teach that results found from the aortic ring bioassay are also found in an in vivo environment.

Applicant alleges that the Kelm, Lundberg and Ignarro declarations cite Lauer et al. which demonstrates that physiological concentrations of nitrite do not cause vasodilation and allegedly shows that vasodilation does not occur in vivo at a concentration of 130 uM. Further, it is alleged that Ignarro is a Nobel Laureate and that the publication of Lauer in PNAS leads one to trust its results. This is not found persuasive. Applicant is drawn to the breadth of claim 1 which recites "*administering* a therapeutically effective amount...." In instant case of Lauer et al., it seems the investigators simply measured endogenous NO concentrations, rather than actually administering sodium nitrite as is recited in the claim. As stated in the rejection above in Remington's Pharmaceutical Sciences, the administration of the salt sodium nitrite, can modify the duration of a drug and the transportation and distribution of the nitrite in the body.

Applicant alleges Lundberg states that the Cosby et al. paper was met with skepticism until the results were reproduced. This is not found persuasive. Though Lundberg's opinion has been noted, in contrast to the allegations cited in the opinion declaration, the art cited above, Shaw et al. and Webb et al. teach the use of nitrite for vasodilatory purposes.

Applicant alleges that the previously cited Pawloski et al. was published after the priority date and as such is not relevant teaching as to what one of ordinary skill in the art would have understood about aortic ring bioassays at the time of the invention. Applicant cites Isbell et al. which allegedly teaches that oxygenated blood inhibits nitrite induced vasodilation of aortic rings which in turn is proof that in vitro experiments are not applicable in vivo. This is not found persuasive. Confusingly, though Applicant states that Pawloski et al. was published after the filing date of the instant application, Applicant themselves cite Isbell et al. which was also published subsequently to the filing of the instant application, in support of the above mentioned allegation. Again, Applicant is guided to the above cited references which teach that results demonstrated in aortic rings were also found in vivo. Arguendo the fact that the Isbell et al. was published subsequently to the filing of the instant application, a review of the

reference, where the primary inventor Mark T. Gladwin is a co-author, does not seem to teach applicant's allegations. In fact the reference teaches, "this study sheds insights into how hemoglobin fractional saturation critically regulates nitrite-dependent NO formation and subsequent vasodilation and further support the concept that vascular functions of nitrite may be controlled by hemoglobin fractional saturation both endogenously and during therapeutic applications" (page H2571, column 1, lines 1-7).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4 and 13-18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 10 and 14-18 of copending Application No. 12/748,184. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the instant invention embraces or is embraced by the subject matter of the copending application. One of ordinary skill in the art would recognize the methods in the copending application of treating hepatic or cardiac or brain ischemia-reperfusion injury by decreasing blood pressure or increasing vasodilation with a non-acidified sodium nitrite to a subject as embracing the

subject matter of instant claims 1-4, 13-15. The same concentrations of sodium nitrite are claimed as well as the subjects and routes of administration.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is found to be allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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